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Commentary

Known effects of levothyroxine and folic acid on serum homocysteine level

This refers to Dr. Ziaee et al.'s manuscript published in your valuable journal about serum homocysteine level entitled "Effects of folic acid plus levothyroxine on serum homocysteine level in hypothyroidism". In this clinical trial study the efficacy of concomitant administration of folic acid and levothyroxine versus single levothyroxine prescription on serum homocysteine level was compared with hypothyroid patients. The authors concluded that "levothyroxine can decrease serum homocysteine level partly; still its combination with folic acid empowers the effect. Combination therapy declines serum homocysteine level more successfully (1)."

Thyroid hormone deficiency is associated with increased cardiovascular events, which cannot be fully explained by the atherogenic changes in lipid profile observed in these patients. Increased homocysteine serum level can help to explain this increased risk in hypothyroidism patients because homocysteine serum level is an important and independent risk factor for cardiovascular disease. Homocysteine is an amino acid which is derived from methionin during its metabolism. Disturbance of methionin metabolism in hypothyroidism has been suggested as the reason of serum homocysteine level rising. Increasing the rate of homocysteine catabolism and diminution of its renal excretion was also reported in patients with hypothyroidism (1, 2).

The association between serum homocysteine level and ischemic heart disease was shown in a cohort study (3). Decrease in serum homocysteine level is expected to decrease the mortality rate of ischemic heart disease about 15% (3, 4).

Hypothyroidism decreases the hepatic levels of enzymes involved in the re-methylation pathway of homocysteine; Therefore, an increased serum homocysteine level is observed in hypothyroid patients even though serum homocysteine is known as a considerable risk factor for cardiovascular system, It is seen that hypothyroidism treatment by levothyroxin will control the cardiovascular risks (2).

A dosage of 1 mg/d has been shown in a meta-analysis to produce the maximum homocysteine reduction. There is a dose-response relationship between serum homocysteine level and prescribed folic acid dose with no further reduction with a higher dosage (5mg/day) (4). This maximum reduction is about 25% (about 3 µmol/L) (4, 5). The patients with higher initial serum homocysteine level are more sensitive in response to prescribed daily folic acid (4, 5).

It seems that using folic acid in conjunction with levothyroxine can decrrease the potential harmful effects of homocysteine on cardiovascular system (1, 6). Based on our clinical experience, there is a clear effect of prescription of folic acid 1 mg/day accompanied with levothyroxine on serum homocysteine reduction.

We fully support the valuable advice of the author, but it should also be noted that high homocysteine serum level in hypothyroid patient is secondary to their underlying pathology (2-4). Therefore, prescription of folic acid after the normalization of thyroid hormones and confirmation of high homocysteine serum level will be a logical advice. We suggest in the hypothyroid patients with high serum homocysteine level a prescription of 1 mg daily folic acid postponded up to 6 weeks after the patients become euthyroid.

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